REMARKS

Reconsideration and allowance of the claims of the present application in view of the amendments and remarks to follow are respectfully requested.

In the Office Action of March 7, 2005, the Examiner has acknowledged applicants' claim for foreign priority under 35 U.S.C. §119(a)-(d) from United Kingdom Application No. 0214784.1 and applicants' claim for priority under U.S.C. §119(e) from provisional application number 60/396,780.

Claims 4-8 are objected to under 37 C.F.R. §1.75(c) as allegedly improper because a multiple dependent claim cannot depend from another multiple dependent claim.

Applicants have amended Claims 4 and 7 to change the dependency of Claim 4 from any preceding claim to Claim 3 and the dependency of Claim 7 from any preceding claim to Claim 1. Support for these amendments can be found at page 4, lines 1-2, page 6, line 24 to page 7, line 6, and page 10, lines 1-3, therefore no new matter is introduced into the present application. The objections to Claims 4-8 have been obviated by these amendments, reconsideration and withdrawal thereof are respectfully requested.

Claim 2 is objected to for allegedly failing to define the abbreviation "IC_{50}" at its first occurrence in the claims.

Applicants have amended Claim 2 to insert a definition of IC_{50} in accordance with the Examiner's suggestion. Support for this amendment can be found in the specification at page 3, lines 31-32, therefore no new matter is introduced into the present application. The objection to Claim 2 has been obviated by this amendment, reconsideration and withdrawal thereof are respectfully requested.

The Examiner states that the previously filed Declaration by the inventors is defective as it fails to acknowledge the filing of any foreign application and misses the residence and postal addresses of the inventors. It is respectfully submitted that a substitute Declaration is in the process of being prepared and executed. As soon as the document is completed, it will be immediately filed with the United States Patent and Trademark Office in a supplemental response to this paper.

The Examiner objects to the title of the invention as allegedly not descriptive. In response, applicants have amended the title to "Pharmaceutical Combinations Comprising a PDE 5 Inhibitor and an Angiotensin II Receptor Antagonist for the Treatment of Hypertension". Applicants submit that the new title is clearly indicative of the invention to which the claims are directed, and thus respectfully request reconsideration and withdrawal of the objection to the title.

The Examiner further objects to the specification for allegedly improper incorporation by reference of International Patent Publications at page 6, lines 1-17.

Applicants have amended the specification to replace the references to International Patent Publications and European Patent Publications with the references to the corresponding U.S. Patents and U.S. Patent Application Publications. Applicants have further included the material incorporated by reference of a journal article and International Patent Publications that do not have corresponding U.S. Patents and U.S. Patent Application Publications. Applicants respectfully refer to the Statement Under 37 C.F.R. §1.57(f) submitted concurrently with the present response, in which it is stated that the material being inserted is the material previously incorporated by reference and the amendment does not introduce new matter into the present application.

Claims 1-3 and 9 are rejected under 35 U.S.C. §101 as allegedly lacking utility. More specifically, the Examiner asserts that Claim 1 recites a use without setting forth any steps involved in the process, thereby results in an improper definition of a process. Claims 1-3 and 9 are further rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to particularly point out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicants have amended Claim 1 to further define the claimed use by setting forth a step involved in the process of use. Support for this amendment can be found at page 11, lines 30-34; page 12, lines 1-9; page 14, lines 5-31; page 15, lines 1-20; page 16, lines 1-14; and page 17, lines 4-8, therefore no new matter is introduced into the present application. The above rejections to Claims 1-3 and 9 have been obviated by this amendment, reconsideration and withdrawal thereof are respectfully requested.

Claims 1-3 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement in the specification.

To expedite prosecution of the present application, applicants have amended Claim 1 to delete the terms "curative or prophylactic", without prejudice. Applicants preserve the right to file a divisional application covering the deleted subject matter. The rejections to Claims 1-3 and 9 under 35 U.S.C. §112, first paragraph, have been obviated by this amendment, reconsideration and withdrawal thereof are respectfully requested.

Claims 1-3, 9-11 and 13 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by the disclosure of U.S. Patent No. 6,087,368 to Macor et al. (hereinafter "Macor et al."). More specifically, the Examiner asserts that Macor et al. teach that the

disclosed cyclic guanosine monophosphate phosphodiesterase (hereinafter "cGMP") PDE5 inhibitor may be employed in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions. Further, the Examiner alleges that Macor et al. disclose the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of both hypertension and atherosclerosis, thus the treatment of hypertension associated with the condition of atherosclerosis, as claimed in the present application, is within the scope of the invention disclosed by Macor et al.

Applicants respectfully submit that the present invention is not anticipated by Macor et al. for the reasons discussed below.

Macor et al. disclose certain quinazolinone compounds, the use thereof in the treatment of cGMP-associated conditions such as erectile dysfunction, and pharmaceutical compositions comprising such compounds. Macor et al. further teach that the compounds disclosed therein are useful for the treatment of a variety of cardiovascular diseases including hypertension and atherosclerosis. However, Macor et al. do not teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension and atherosclerosis, as alleged by the Examiner. In fact, Macor et al. merely disclose, in general terms and without any substantial evidence, that the compounds disclosed therein may be employed in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions (See Macor et al., column 18, lines 60-67). Macor et al. do not specifically disclose which cGMP-associated conditions can be treated with the combined use of the disclosed compounds and other suitable therapeutic agents. In contrast, the present invention is directed to the use of combination of an inhibitor of cGMP PDE5 and

an angiotensin II receptor antagonist for the treatment of hypertension, including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis and renovascular hypertension, congestive heart failure, angina, stroke, diabetes and impaired glucose tolerance.

It is axiomatic that anticipation requires that the cited reference teach each and every limitation of the claimed invention to which the reference is applied. In the present case, Macor et al. fail to teach all the limitations of Claim 1, thus Macor et al. do not anticipate Claim 1 and the dependent claims thereof.

The rejections under §102(b) have been obviated, thus reconsideration and withdrawal thereof are respectfully requested.

Claims 1-3 and 9-13 are rejected under 35 U.S.C. §103(a) as unpatentable over Marcor et al. in view of The Merck Manual of Diagnosis and Therapy, 16th Edition, 1992, 413-431 (hereinafter "the Merck Manual"), Cecil Textbook of Medicine, 21st Edition, Vol. 1, 2000, 273-279 and 1279-1285 (hereinafter "Cecil"), and Physician's Desk Reference, 55th Edition, 2001, 323 and 330 (hereinafter "Physician's Desk Reference"). More specifically, the Examiner alleges that Macor et al. broadly disclose the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension, and the Merck Manual and Cecil teach various types of hypertension, as recited in Claim 1. The Examiner therefore concludes that it would have been obvious to one skilled in the art at the time of the invention to use a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of various types of hypertension as claimed in the present application.

Applicants respectfully submit that the Examiner fails to establish a *prima facie* case of obviousness as discussed below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the cited reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the reference, not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, the cited references, solely or in combination, do not teach or remotely suggest the claimed invention. As discussed previously, although Macor et al. disclose, in general terms and without any substantial evidence, that the compounds disclosed therein may be employed in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions, Macor et al. do not teach the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of hypertension and atherosclerosis, as alleged by the Examiner. The Merck Manual and Cecil teach various types of hypertension, but do not teach or remotely suggest the use of a cGMP PDE5 inhibitor in combination with an angiotensin II antagonist for the treatment of the various types of hypertension disclosed therein.

Second, there is no motivation in the cited references available to one skilled in the art which suggests a combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist for the treatment of various types of hypertension. The

disclosure of Macor et al., as a whole, focuses on certain quinazolinone compounds and the use thereof in the treatment of cGMP-associated conditions, particularly erectile dysfunction (See Macro et al., columns 1-4). Macor et al. further disclose, in general terms and without any substantial evidence, that the compounds disclosed therein may be employed in combination with other suitable therapeutic agents useful in the treatment of cGMP-associated conditions (See Macor et al., column 18, lines 60-67). However, Macor et al. fail to teach or remotely suggest the specific diseases or conditions that can be treated by the combined use of the disclosed compounds and other suitable therapeutic agents. In contrast, the present application presents data on page 20 demonstrating that the efficacy of the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist is significantly larger than the sum of the additive effects thereof. Applicants submit that the broad disclosure of Macor et al. is merely based on the common knowledge in the art that additive therapeutic effects may be obtained by administering to a patient multiple drugs in combination.

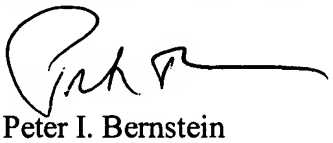
In addition, neither the Merck Manual nor Cecile suggests the combined use of a cGMP PDE5 inhibitor and an angiotensin II antagonist. Therefore, applicants submit that one skilled in the art, in view of the cited reference, would not be motivated to combine a cGMP PDE5 inhibitor and an angiotensin II antagonist in the treatment of the various types of hypertension, as claimed in the present application. Thus, there is no motivation provided in the applied references, or otherwise of record, to make and use the combination therapy as mentioned above. "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification

obvious unless the prior art suggested the desirability of the modification." In re Vaeck, 947 F.2d, 488, 493, 20 USPQ 2d. 1438, 1442 (Fed.Cir. 1991).

The rejection under 35 U.S.C. §103 has been obviated; therefore reconsideration and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remark, it is firmly believed that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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